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Clinical and bacteriological outcomes in hospitalised patients with community-acquired pneumonia treated with azithromycin plus ceftriaxone, or ceftriaxone plus clarithromycin or erythromycin: a prospective, randomised, multicentre study

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ABSTRACT

This study compared patients with moderate-to-severe community-acquired pneumonia (CAP) requiring hospitalisation, who received initial therapy with either intravenous ceftriaxone plus intravenous azithromycin, followed by step-down to oral azithromycin (n = 135), with patients who received intravenous ceftriaxone combined with either intravenous clarithromycin or erythromycin, followed by step-down to either oral clarithromycin or erythromycin (n = 143). Clinical and bacteriological outcomes were evaluated at the end of therapy (EOT; day 12–16) or at the end of study (EOS; day 28–35). At baseline, mean APACHE II scores were 13.3 and 12.6, respectively, with >50% of patients classified as Fine Pneumonia Severity Index (PSI) category IV or V. Clinical success rates (cure or improvement) in the modified intent-to-treat (MITT) population at EOT were 84.3% in the ceftriaxone/azithromycin group and 82.7% in the ceftriaxone/clarithromycin or erythromycin group. At EOS, MITT success rates (cure only) were 81.7% and 75.0%, respectively. Equivalent success rates in the clinically evaluable population were 83% and 87%, respectively, at EOT, and 79% and 78%, respectively, at EOS. MITT bacteriological eradication rates were 73.2% and 67.4%, respectively, at EOT, and 68.3% vs. 60.9%, respectively, at EOS. Mean length of hospital stay (LOS) was 10.7 and 12.6 days, and the mean duration of therapy was 9.5 and 10.5 days, respectively. The incidence of infusion-related adverse events was 16.3% and 25.2% (p 0.04), respectively. An intravenous-to-oral regimen of ceftriaxone/azithromycin was at least equivalent in efficacy and safety to the comparator regimen and appeared to be a suitable treatment option for hospitalised patients with CAP.

Keywords Azithromycin, ceftriaxone, clarithromycin, community-acquired pneumonia, erythromycin, therapy

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INTRODUCTION

Community-acquired pneumonia (CAP) remains a significant cause of morbidity and mortality worldwide. Effective medical intervention requires that initial antimicrobial therapy is active against the causative organism(s), but identification of the pathogen remains undetermined at the time therapy is initiated in most cases. Bacteriological culture results are positive in <50% of hospitalised patients, even in the idealised setting of prospective studies [1]. In data from 26 prospective studies conducted in ten western European countries, the most common causative pathogen in 5961 patients hospitalised with CAP

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was *Streptococcus pneumoniae*, followed by the atypical pathogens *Chlamydophila* (*Chlamydia*) *pneumoniae*, *Mycoplasma pneumoniae* and *Legionella* spp. [2]. Accordingly, empirical therapy for CAP is usually directed against these pathogens [3,4]. As atypical pathogens, e.g., *C. pneumoniae*, *M. pneumoniae* and *Legionella* spp., have been found to be common in patients with CAP in some studies, many investigators recommend that empirical antibiotic treatment should cover these organisms [5].

Several treatment guidelines, including those of the European Respiratory Society (ERS) Task Force [6], the American Thoracic Society (ATS) [7] and the Infectious Diseases Society of America (IDSA) [8], include a β-lactam/macrolide combination for the treatment of hospitalised patients with CAP. For management of a patient in the general medical ward, current ERS guidelines recommend first-line therapy with a second- or third-generation cephalosporin, β-lactam/β-lactamase inhibitor, benzyl penicillin, amoxycillin or ampicillin, with the option of adding a macrolide such as intravenous erythromycin, oral azithromycin (also classed as an azalide) or clarithromycin. For the patient in an intensive care unit (ICU), a second- or third-generation cephalosporin plus a second-generation quinolone or macrolide is recommended, with the option of adding rifampicin [6]. North American guidelines for the empirical treatment of CAP patients recommend inclusion of macrolides to provide coverage of atypical pathogens, irrespective of the risk stratification of the patient [7,8]. Linezolid is also effective for hospitalised patients with CAP [9], and the recent IDSA guidelines for hospital-acquired, ventilator-associated or healthcare-associated pneumonia recommend linezolid for patients at high risk of methicillin-resistant *Staphylococcus aureus* (MRSA) [10].

In Europe, ceftriaxone is used widely for the empirical treatment of CAP, with the addition of an intravenous macrolide such as erythromycin or clarithromycin. Macrolide and azalide antibiotics provide coverage of the main bacterial pathogens, as well as atypical pathogens, that are implicated in CAP [11–14]. Studies have shown that the inclusion of a macrolide with a second- or third-generation cephalosporin regimen can reduce mortality and length of stay in patients hospitalised with CAP [1,14–16]. The prototypical macrolide, erythromycin, has a number of disadvantages that include varying degress of oral absorption, the need for multiple daily dosing, high rates of gastrointestinal adverse events, and sub-optimal antimicrobial activity against the Gram-negative CAP pathogen *Haemophilus influenzae* and the atypical CAP pathogen *C. pneumoniae* [17,18]. The chemical modification of azithromycin gives it pharmacokinetic advantages compared with other macrolides, including improved oral bioavailability, tissue distribution and prolonged elimination half-life, thereby allowing convenient once-daily dosing [19]. Moreover, azithromycin provides coverage for all common CAP pathogens including *Strep. pneumoniae*, *H. influenzae*, *Moraxella catarrhalis* [11], *C. pneumoniae*, *M. pneumoniae* and *Legionella* spp. [20]. Azithromycin has also shown superior in-vitro activity against *H. influenzae* and *Morax. catarrhalis* compared with clarithromycin and erythromycin [21].

Retrospective studies published recently have reported that macrolide-containing regimens are associated with improved survival in CAP patients [22] and decreased lengths of hospital stay [23]. The aim of the present investigation was to examine the clinical and bacteriological efficacy and safety in patients with moderate-to-severe CAP requiring hospitalisation who received initial therapy with either intravenous ceftriaxone plus intravenous azithromycin, followed by step-down to oral azithromycin, or intravenous ceftriaxone, combined with either intravenous clarithromycin or erythromycin, followed by step-down to either oral clarithromycin or erythromycin.

MATERIALS AND METHODS

Study design

This multicentre study was a prospective, randomised and open-label clinical trial conducted between April 2002 and March 2003 in Austria, Belgium, Finland, France, Germany, Israel, Italy, The Netherlands, Portugal, South Africa, Spain, Switzerland and Turkey. Patients with CAP requiring hospitalisation were assigned randomly to either: (i) intravenous ceftriaxone 1–2 g once-daily plus intravenous azithromycin 500 mg once-daily for 2–5 days, followed by step-down to oral azithromycin 500 mg once-daily for a total therapy duration of 7–10 days; or (ii) intravenous ceftriaxone 1–2 g once-daily plus either intravenous clarithromycin 500 mg twice-daily or erythromycin 1 g three times a day for 2–5 days, followed by step-down to either oral clarithromycin 500 mg twice-daily or erythromycin 1 g three times a day for a total of 7–14 days. Erythromycin was substituted for clarithromycin in those countries (France, Germany, Israel and The Netherlands) that

do not have approval for intravenous clarithromycin for the treatment of CAP. Subjects were assigned randomly to treatment groups in a ratio of 1:1.

Patients

Male and female patients, aged ≥18 years, with clinical and radiological findings consistent with a community-acquired bronchopneumonia or lobar pneumonia that required hospitalisation and initial intravenous antibiotic therapy, were eligible for enrolment. Specific inclusion criteria were the radiographical appearance of a new pulmonary infiltrate and at least two of the following: cough or increasing severity of coughing; acute changes in sputum quality; oral body temperature or equivalent >38°C or <36.1°C, or documented fever or hypothermia within the past 24 h; auscultatory findings, such as rales or evidence of pulmonary consolidation; dyspnoea, tachypnoea, or hypoxaemia; and leukocytosis, defined as a white blood cell count >10 000/mm^3 or >15% immature neutrophils/bands. In addition, eligible patients had a minimum APACHE II score of 8.

Patients who presented with any of the following conditions were excluded: females who were pregnant or lactating, or of childbearing age and not using adequate contraception; treatment with any systemic antibiotic for ≥24 h within 72 h of baseline visit, or treatment for >7 days within the past month unless there was documented evidence of clinical or bacteriological failure; life expectancy of ≤48 h; AIDS or suspected *Pneumocystis carinii* pneumonia; significant neutropenia; radiological evidence of cavitary lung disease, primary lung cancer or metastatic lung malignancy, aspiration pneumonia, empyema or tuberculosis; cystic fibrosis; progressive neoplastic disease; a history of epilepsy or seizure; or bronchiectasis, bronchial obstruction or a history of post-obstructive pneumonia. Also excluded were patients who were already hospitalised or who had resided in a long-term care facility for >14 days before the onset of symptoms. Written informed consent was obtained from all patients, and the study received approval from the institutional review board at each participating centre, in compliance with Good Clinical Practice (GPC), including the International Conference on Harmonisation (ICH) Guidelines, and the most recent version of the Declaration of Helsinki.

Study visits and procedures

The initial baseline visit (day 1) occurred ≤24 h before the first dose of study medication, and included eligibility screening, taking of a medical history, a physical examination, assessment of APACHE II and Fine Pneumonia Severity Index (PSI) scores, and pregnancy testing. Assessments for previous antibiotic use, concomitant medication, healthcare utilisation, vital signs and clinical signs and symptoms were performed on day 1, daily during hospitalisation, at the end of therapy (EOT; day 12–16) and at the end of study (EOS; day 28–35). Sputum samples for Gram's stain (an adequate sputum sample was defined as one containing >25 polymorphonuclear leukocytes and <10 squamous epithelial cells/low power field of a stained specimen), culture and susceptibility testing, and blood samples for haematology and biochemistry tests, were obtained on days 1 and 3, at EOT and EOS. Blood samples for culture were taken at baseline and at other intervals when a previous positive blood culture had been observed. Chest X-rays were performed on day 1 and again at EOS; urine samples were obtained on day 1 for detection of *Strep. pneumoniae* and *Legionella* urinary antigens; serum samples were obtained on day 1 and at EOS for detection of *M. pneumoniae*, *Legionella* spp., *C. pneumoniae* and *Chlamydophila psittaci*; and pharyngeal swabs were obtained on day 1 and at EOS for detection of *C. pneumoniae*, *M. pneumoniae* and *Legionella* spp. by PCR [24–27]. Assessment for oral step-down was made on day 3, with patients being switched to oral therapy if the following criteria were satisfied: oral temperature or equivalent <37.8°C for >8 h; cough and shortness of breath improvement; adequate oral intake and gastrointestinal absorption; and white blood cell count normalising. Finally, assessment for adverse events took place daily during hospitalisation and at EOT and EOS.

Detection of atypical pathogens

Serological testing for atypical pathogens was performed by MDS Pharma Services (Paris, France). Positive IgG serology was defined as a single titre ≥1:256 for *M. pneumoniae*, ≥1:512 for *C. pneumoniae*, ≥1:128 for *Legionella pneumophila* and ≥1:128 for *C. psittaci*. PCR testing for atypical pathogens was undertaken at baseline (day 1). Pharyngeal swab specimens were tested using PCR for *C. pneumoniae*, *M. pneumoniae* and *Legionella* spp. by F. Blasi (University of Milan, Milan, Italy) [24–27]. Touchdown nested PCR was performed using primers designed to detect the major outer-membrane protein of *C. pneumoniae* [24,25], which allows the detection of *c.* 1–5 *C. pneumoniae* elementary bodies. PCR was performed using the MP8 sense primer and the MP6 antisense primer, selected from a variable region of the *M. pneumoniae* 16S rRNA genome [26]. This PCR technique had a lower detection limit of ten *M. pneumoniae* genome equivalents.

Evaluations

Clinical evaluation of response was based on the investigator's global assessment of radiological findings and the clinical signs and symptoms, including dyspnoea, cough, sputum volume and character, and fever. Clinical response was classified following baseline comparison as cure or failure at EOS, or as cure, improvement or failure at EOT, according to the following definitions: 'cure', resolution of signs and symptoms of pneumonia; 'improvement', resolution of fever, but incomplete resolution of other signs and symptoms of pneumonia and no requirement for additional antibiotic treatment; 'failure', lack of resolution or deterioration of any signs and symptoms of pneumonia, and a need for additional antibiotic treatment. Bacteriological response was classified as eradication or persistence of the original causative organism(s) at EOT and EOS. All treated patients with a medical history and clinical and radiological findings consistent with CAP were included in the clinical modified intent-to-treat (MITT) population. A clinically evaluable subgroup excluded MITT patients who had received <3 days of study medication, or >120% of the prescribed study medication, or concomitant systemic antibiotic treatment for intercurrent illness, or who had missed an evaluation. Analysis of bacteriological response included those patients in the clinical MITT population who had at least one causative pathogen isolated at baseline (bacteriological MITT population), as well as a separate evaluable population comprising the bacteriological MITT population who were also considered clinically evaluable.

The primary efficacy endpoint was clinical response at EOS for the clinically evaluable patient population. Secondary endpoints were: clinical response at EOT for clinically evaluable patients; clinical response at EOT and EOS for MITT patients; and bacteriological response at EOT and EOS for bacteriological MITT and bacteriological evaluable patients. The length of hospital stay (LOS), total duration of therapy, and safety and tolerability of the two treatment regimens, were also assessed. All randomised subjects who received at least one dose of study medication were included for analysis of safety and tolerability.

Statistical analysis

In order to establish equivalency between ceftriaxone plus azithromycin, and ceftriaxone plus clarithromycin/erythromycin, for the treatment of CAP in moderate-to-severely-ill hospitalised patients, a two-sided 95% CI for the difference in the rate of clinical and bacteriological response to the two regimens was calculated. The reference for the comparator group was estimated to be 90%, the α-level (or value) was 0.05 and the power (b or β-value) was 0.2. Ceftriaxone plus azithromycin was deemed to be non-inferior to the comparator regimen if the lower limit of this calculation was ≥ 10%.

RESULTS

Demographics

The baseline demographical characteristics of the 278 hospitalised patients who received treatment for CAP were comparable for patients in the two treatment groups (Table 1). Of 143 patients who were administered ceftriaxone plus clarithromycin/erythromycin, 109 received clarithromycin and 34 received erythromycin.

Thirty-eight patients in the ceftriaxone plus azithromycin group, and 47 patients in the ceftriaxone plus clarithromycin/erythromycin group, were infected with an atypical pathogen (*C. pneumoniae*, *M. pneumoniae* or *Legionella* spp.), or an atypical pathogen plus a conventional bacterial pathogen, identified by serology or PCR at baseline or EOS, equivalent to 32.1% of the 265 patients from whom serum samples and pharyngeal swabs were available. In total, 61 (23.0%) patients were infected with an atypical pathogen alone, and 24 (9.1%) patients were infected with an atypical pathogen plus a conventional bacterial pathogen. *M. pneumoniae* was the atypical pathogen identified most commonly (16.2%), followed by *C. pneumoniae* (10.9%) and *Legionella* spp. (6.0%).

Table 1. Patient demographics

	CEF/AZM	CEF/C or E
Total no.	135	143
Male, *n* (%)	94 (70)	97 (68)
Female, *n* (%)	41 (30)	46 (32)
Age		
Mean, years (SD)	64.2 ± 17.1	62.4 ± 18.7
>65 years, *n* (%)	85 (63)	82 (57)
Smoking history		
Smoker	30 (22)	54 (38)[a]
Ex-smoker	62 (46)	47 (33)
Never smoked	42 (31)	42 (29)
Mean APACHE score ± SD	13.3 ± 4.3	12.6 ± 4.1
Mean Fine PSI ± SD	91.8 ± 27.2	92.2 ± 26.0
Fine PSI category, *n* (%)		
I or II (<71)	27 (20)	33 (23.1)
III (71–90)	37 (27.4)	37 (25.9)
IV (91–130)	62 (45.9)	65 (45.5)
V (>131)	9 (6.7)	8 (5.6)

CEF, ceftriaxone; AZM, azithromycin; C, clarithromycin; E, erythromycin; SD, standard deviation; PSI, pneumonia severity index.
[a]p 0.05.

Clinical response

In the clinically evaluable population, the clinical response to ceftriaxone plus azithromycin, and ceftriaxone plus clarithromycin/erythromycin, was similar at both EOS and EOT (Fig. 1). The more stringent MITT analysis, in which missing values were counted as failures, showed that success rates were similar to those observed in the clinically evaluable population. Clinical success rates at EOT were 84.3% for ceftriaxone plus azithromycin, and 82.7% for ceftriaxone plus clarithromycin/erythromycin. Success rates at EOS (cure only) were 81.7% for ceftriaxone plus azithromycin, and 75.0% for ceftriaxone plus clarithromycin/erythromycin. When Fine PSI categories and APACHE II scores were used to classify patients according to disease severity, there were no major differences in clinical success rates between patients in either treatment group (Table 2).

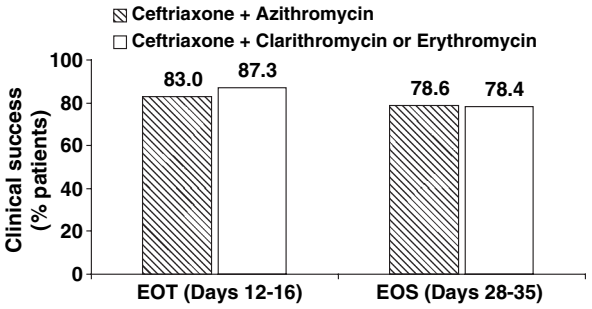

Fig. 1. Clinical success at end of therapy (EOT; cure or improvement) and end of study (EOS; cure only) in the clinically evaluable population (one subject infected with an atypical pathogen and a conventional bacterial pathogen was randomised to receive azithromycin but actually received erythromycin).

Table 2. Clinical responses at end of therapy (EOT) according to disease severity classified by APACHE score and Fine PSI category

	Clinical MITT response at EOT		
	95% CI	CEF/AZM	CEF/C or E
APACHE II score			
5–9	87.5% (21/24)	87.9% (29/33)	–
10–14	84.7% (50/59)	78.6% (44/56)	–
15–19	85.2% (23/27)	86.2% (25/29)	–
20–24	85.7% (6/7)	75.0% (6/8)	–
25–30	50.0% (2/4)	–	–
Fine PSI category			
III	77.1 (27/35)	80% (28/35)	– 22.1%, 16.4%
IV	86.8% (46/53)	82.1% (46/52)	– 8.9%, 18.2%
V	77.8% (7/9)	85.7% (6/7)	– 45.5%, 29.6%

AZM, azithromycin; CEF, ceftriaxone; C, clarithromycin; E, erythromycin; MITT, modified intent-to-treat; PSI, pneumonia severity index.

Symptom resolution was also similar for patients treated with ceftriaxone plus azithromycin, or ceftriaxone plus clarithromycin/erythromycin. Based on signs and symptoms at baseline that affected >80% of the clinical MITT population, cough, dyspnoea, rales and sputum production were still observed at EOS in 23.7%, 22.9%, 16.2% and 19.0%, respectively, of the ceftriaxone plus azithromycin group, compared with 30.0%, 19.5%, 22.3% and 16.8% of the ceftriaxone plus clarithromycin/erythromycin group.

Bacteriological response

In total, 87 (31.3%) patients in the two treatment groups had a pathogen associated with respiratory illness isolated at baseline, and were included in the bacteriological MITT population. The pathogens isolated most frequently at baseline were *Strep. pneumoniae*, *H. influenzae* and *Staph. aureus*. Of those patients in the bacteriological MITT population who received treatment with ceftriaxone plus azithromycin, or ceftriaxone plus clarithromycin/erythromycin, *Strep. pneumoniae* was isolated from 44% and 57% of patients, respectively, *H. influenzae* from 25% and 18%, respectively, and *Staph. aureus* from 13% and 4%, respectively. Other organisms identified at baseline included *Haemophilus parainfluenzae* (6%, 9%), *Pseudomonas aeruginosa* (6%, 4%) and *Morax. catarrhalis* (2%, 2%). Thirteen patients in the azithromycin plus ceftriaxone group, and ten patients in the ceftriaxone plus clarithromycin/erythromycin group, had more than one pathogen isolated at baseline.

Table 3 summarises bacteriological eradication in both the bacteriological MITT and evaluable populations, and clinical success according to baseline pathogen in the bacteriological MITT population. Bacteriological eradication rates at EOT and EOS were similar for the two treatment groups in the bacteriological evaluable population. However, in the bacteriological MITT population, bacteriological eradication rates were superior (not significant) at both EOT and EOS for the ceftriaxone plus azithromycin group (73.2% and 68.3%, respectively) compared with the ceftriaxone plus clarithromycin/erythromycin group (67.4% and 60.9%, respectively). When clinical success was determined according to baseline pathogen, treatment with ceftriaxone plus azithromycin, or ceftriaxone plus clarithromycin/erythromycin, demonstrated equivalent clinical success rates in patients with *Strep. pneu-*

Table 3. Clinical success determined according to bacteriological eradication in the bacteriological modified intent-to-treat (MITT) and evaluable populations, or according to baseline pathogen in the bacteriological MITT population and in patients with atypical pathogens

	EOT (day 12–16)		EOS (day 28–35)	
Outcome	CEF/AZM % (*n*)	CEF/C or E % (*n*)	CEF/AZM % (*n*)	CEF/C or E % (*n*)
Bacteriological eradication				
MITT population	73.2 (30/41)	67.4 (31/46)	68.3 (28/41)	60.9 (28/46)
Evaluable	80.0 (24/31)	80.6 (25/31)	72.7 (16/22)	74.2 (23/31)
Clinical success by baseline pathogen[a] in bacteriological MITT population				
Streptococcus pneumoniae	81.0 (17/21)	70.0 (21/30)	75.0 (15/20)	66.7 (20/30)
Haemophilus influenzae	92.3 (12/13)	50.0 (4/8)	92.3 (12/13)	37.5 (3/8)
Staphylococcus aureus	83.3 (5/6)	100 (1/1)	83.3 (5/6)	100 (1/1)
Clinical success in patients with atypical pathogens in clinical MITT population				
Mycoplasma pneumoniae	88.9 (8/9)	77.8 (7/9)	88.9 (8/9)	77.8 (7/9)
Chlamydia pneumoniae	100.0 (6/6)	77.8 (7/9)	100.0 (8/8)	66.7 (6/9)
Legionella spp.	50.0 (1/2)	71.4 (5/7)	0 (0/1)	75.0 (6/8)
Clinical success in patients with positive blood cultures				
MITT	66.7 (8/12)	58.8 (10/17)[b]	66.7 (8/12)	52.9 (9/17)[b]

CEF, ceftriaxone; AZM, azithromycin; C, clarithromycin; E, erythromycin; EOT, end of therapy; EOS, end of study.
[a]Nineteen patients had two or more pathogens at baseline (six and four patients were cured in the CEF/AZM and CEF/C or E groups, respectively).
[b]Not significantly different compared with CEF/AZM.

moniae or *Staph. aureus* as a baseline pathogen. Although the number of evaluable patients was relatively small, there was a trend towards improved clinical success in patients with *H. influenzae* as a baseline pathogen who were treated with ceftriaxone plus azithromycin. At EOS, clinical success in response to *H. influenzae* was observed in 12 (92.3%) of 13 patients treated with ceftriaxone plus azithromycin, compared with three (37.5%) of eight patients treated with ceftriaxone plus clarithromycin/erythromycin. Clinical success was observed at both EOT and EOS for one patient from each treatment group with *Morax. catarrhalis* isolated at baseline (data not shown). In the population of patients with severe illness (Fine PSI categories IV and V) and positive baseline cultures, 42 patients were evaluable; clinical cure was observed in 20 (90.9%) of 22 patients treated with ceftriaxone plus azithromycin, compared with 14 (70.0%) of 20 patients who received ceftriaxone plus clarithromycin/erythromycin.

There was a small number of patients in the bacteriological MITT population from whom *Strep. pneumoniae* was isolated from the baseline blood cultures. Bacteriological success rates were similar in both treatment groups at EOT and EOS (Table 4).

In patients with an atypical pathogen only, clinical success (cure) at EOS was observed in a higher proportion (not significant) of patients treated with ceftriaxone plus azithromycin (18 of 20; 90%) compared with patients who received ceftriaxone plus clarithromycin/erythromycin (24 of 30; 80%). In patients with both an atypical pathogen and a conventional bacterial pathogen, nine (90%) of ten patients treated with ceftriaxone plus azithromycin showed a clinical cure, compared with six (54.5%) of 11 patients treated with ceftriaxone plus clarithromycin/erythromycin. Clinical success at EOT was higher with ceftriaxone plus azithromycin, with 17 (89.5%) of 19 patients with an atypical pathogen, and ten (90.9%) of 11 patients with both an atypical and a conventional bacterial pathogen, showing clinical cure, compared with 24 (80.0%) of 30 and seven (63.6%) of 11 patients treated with ceftriaxone plus clarithromycin/erythromycin.

Table 4. Bacteriological response in patients with *Streptococcus pneumoniae* isolated from baseline blood culture (bacteriological modified intent-to-treat population; *n* (%) of patients)

Visit	Bacteriological response	CEF/AZM	CEF/C or E
Subjects evaluable at the EOT visit	12 (100)	17 (100)	
EOT (Visit 3)	Success	8 (66.7)	12 (70.6)
	Eradication	3	3
	Presumed eradication	5	9
	Failure	4 (33.3)	5 (29.4)
	Presumed persistence	2	5
	Persistence	0	0
	Unknown	2	0
Subjects evaluable at the EOS visit	12 (100.0)	17 (100.0)	
EOS (Visit 4)	Success	7 (58.3)	9 (52.9)
	Eradication	4	2
	Presumed eradication	3	7
	Failure	5 (41.7)	8 (47.1)
	Presumed persistence	3	8
	Unknown	2	0

CEF, ceftriaxone; AZM, azithromycin; C, clarithromycin; E, erythromycin; EOT, end of therapy; EOS, end of study.

Healthcare resource utilisation

Analysis of healthcare utilisation data indicated an advantage (not significant) for treatment with ceftriaxone plus azithromycin, compared with ceftriaxone plus clarithromycin/erythromycin, for hospitalised patients with CAP. In the group treated with ceftriaxone plus azithromycin, the mean (± SD) hospital LOS was 10.7 (6.8) days, compared with 12.6 (10.8) days for patients treated with ceftriaxone plus clarithromycin/erythromycin. There was also an advantage (not significant) in treatment with ceftriaxone plus azithromycin in terms of mean duration of therapy, with a total duration of intravenous and oral therapy of 9.5 days, compared with 10.5 days for patients treated with ceftriaxone plus clarithromycin/erythromycin. The mean time from intravenous initiation to oral switch was 5.0 days for patients treated with ceftriaxone plus azithromycin, and 4.7 days for patients treated with ceftriaxone plus clarithromycin/erythromycin.

Patients with an atypical pathogen, or an atypical pathogen and a conventional bacterial pathogen, had a reduction in mean hospital LOS of 3.6 days and 3.3 days, respectively, when treated with ceftriaxone plus azithromycin, compared with ceftriaxone plus clarithromycin/erythromycin (Fig. 2). Patients with an atypical pathogen, or an atypical pathogen and a conventional bacterial pathogen, also had a shorter mean duration of intravenous and oral therapy when treated with ceftriaxone plus azithromycin, compared with ceftriaxone plus clarithromycin/erythromycin (atypical pathogen, 9.2 vs. 10.3 days, respectively; atypical plus conventional

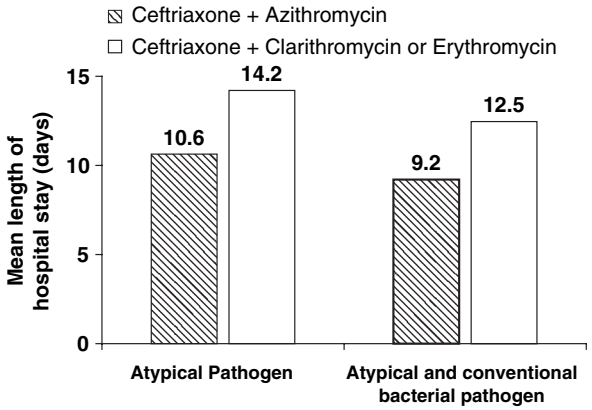

Fig. 2. Mean length of hospital stay for patients in the two treatment groups with an atypical pathogen, or an atypical and a conventional bacterial pathogen, identified during the course of the study.

bacterial pathogen, 9.3 vs. 10.1 days, respectively). This reduction was attributable largely to a reduction in the mean duration of oral dosing of 0.8 days (atypical pathogen) and 1.2 days (atypical plus conventional bacterial pathogen) when patients were treated with ceftriaxone plus azithromycin, compared with ceftriaxone plus clarithromycin/erythromycin.

Safety and tolerability

Overall, a slightly lower proportion of patients treated with ceftriaxone plus azithromycin reported a treatment-related adverse event (44/135, 32.6%) compared with those treated with ceftriaxone plus clarithromycin/erythromycin (58/143, 40.6%). All adverse events in the ceftriaxone plus azithromycin group were classified as mild or moderate in severity. Three adverse events in the ceftriaxone plus clarithromycin/erythromycin group were classified as severe, comprising injection site inflammation (the subject discontinued participation in the study), injection site pain (intravenous erythromycin was discontinued and the patient was switched to oral erythromycin) and hepatic enzyme increase (no action was taken).

As shown in Table 5, significantly more patients in the ceftriaxone plus clarithromycin/erythromycin group reported infusion-related adverse events compared with patients treated with ceftriaxone plus azithromycin (23.8% vs. 14.1%, p 0.04). Among patients treated with ceftriaxone plus clarithromycin/erythromycin, 24 (22.0%) of 109 patients in the clarithromycin arm, and ten (29.4%) of 34 patients in the erythromycin arm, reported infusion-related adverse events. Most infusion-related adverse events were mild in severity, but two (5.9%) of 34 patients treated with ceftriaxone plus clarithromycin/erythromycin reported severe infusion-related adverse events, compared with none in the ceftriaxone plus azithromycin group. Infusion-related adverse events persisted for a similar mean length of time in the two groups: 4.4 (3.9) days in the ceftriaxone plus azithromycin group, compared with 4.7 (5.6) days in the ceftriaxone plus clarithromycin/erythromycin group.

Table 5. Treatment-related adverse events affecting patients in the two treatment groups

	CEF/AZM (total *n* = 135) *n* (%)	CEF/C or E (total *n* = 143) *n* (%)
Infusion-related events		
Application site infection/inflammation	14 (14.1)	34 (23.8)
Application site pain	2 (1.5)	9 (6.3)
Gastrointestinal events	17 (12.6)	26 (18.2)
Diarrhoea	10 (7.4)	12 (8.4)
Nausea	2 (1.5)	7 (4.9)
Hepatic enzymes increased	4 (3.0)	4 (2.8)

CEF, ceftriaxone; AZM, azithromycin; C, clarithromycin; E, erythromycin.

Gastrointestinal adverse events were reported by 17 (12.6%) of 135 patients treated with ceftriaxone plus azithromycin, compared with 26 (18.2%) of 143 patients treated with ceftriaxone plus clarithromycin/erythromycin. As shown in Table 5, diarrhoea was the intestinal adverse event reported most frequently, affecting similar proportions of patients in each treatment group. One patient in the ceftriaxone plus azithromycin group discontinued treatment because of elevated hepatic enzyme levels, while four patients in the ceftriaxone plus clarithromycin/erythromycin group discontinued treatment because of: (i) cutaneous erythematous eruption; (ii) anorexia, emesis, urticaria and taste perversion; (iii) emesis and hearing loss on left side; and (iv) phlebitis of left hand at the infusion site. Finally, there were seven deaths in the ceftriaxone plus azithromycin group, and five deaths in the ceftriaxone plus clarithromycin/erythromycin group, either during the study or within 35 days of the final dose of treatment. None of these deaths was considered to be treatment related.

DISCUSSION

This study demonstrates that treatment of patients who require hospitalisation because of

moderate-to-severe CAP with initial intravenous ceftriaxone plus azithromycin, followed by oral azithromycin, is equal in efficacy and safety to a standard regimen of intravenous ceftriaxone plus either clarithromycin or erythromycin, followed by step-down to oral clarithromycin or erythromycin. Using the more stringent criteria of MITT, where subjects with missing clinical outcome data were classified as therapeutic failures, the clinical cure rate was at least as good as that obtained with the comparator therapy at EOS. In addition, ceftriaxone plus azithromycin therapy achieved equivalent clinical success at EOT, independent of the APACHE II score or PSI category. However, the lower number of subjects in the Fine PSI category III and V groups meant that these data are associated with larger CIs.

Bacterial eradication and clinical success by baseline pathogen were equivalent for the two antimicrobial regimens, although there was a non-significant effect favouring ceftriaxone plus azithromycin for patients with *H. influenzae* isolated at baseline. Atypical coverage also favoured ceftriaxone plus azithromycin, with higher clinical success rates (not significant) at both EOT and EOS, compared with ceftriaxone plus clarithromycin/erythromycin. In the patients who had a positive blood culture at baseline, the clinical response rates did not differ between the two groups. Furthermore, ceftriaxone plus azithromycin had a comparable overall safety profile, with fewer infusion-related adverse events (p 0.04). Causative pathogens cannot be identified in 50–60% of CAP patients, even when extensive testing is undertaken [1,28–31]. In the present study, causative pathogens were identified in 53% of subjects at baseline (22% of patients were positive for an atypical respiratory pathogen alone using serology and PCR testing), which is consistent with other studies.

Updated clinical guidelines have delineated a role for azithromycin as oral therapy in outpatients [7,8], as oral therapy in combination with an intravenous cephalosporin for use in the medical ward [6], as intravenous therapy for use in the medical ward, either alone [7] or in combination with a cephalosporin [8], and in the ICU in combination with a cephalosporin [7,8]. In comparison with a standard therapeutic regimen that followed American Thoracic Society (ATS) guidelines, azithromycin has been shown to be as effective and at least as safe when administered as initial intravenous therapy to hospitalised patients with CAP, either as monotherapy [3,13,32] or in combination with a cephalosporin [33]. The combination of a macrolide and a cephalosporin has been associated with improved patient outcomes, which include reduced mortality [1,14–16] and LOS [15]. Adverse events were significantly less common with azithromycin-containing regimens than with regimens containing erythromycin, with the latter being associated with higher rates of gastrointestinal disturbances and infusion-related events [3,13], which reflects the findings of the present investigation.

The use of azithromycin together with a cephalosporin may have advantages over other macrolide/cephalosporin combinations, as dosing is once-daily. Combined with a lower rate of gastrointestinal disturbance, this may improve compliance in patients switched to oral therapy [6,19]. Notable microbiological features of azithromycin are superior in-vitro activity against *H. influenzae* compared with both erythromycin and clarithromycin [11,21,34], and superior activity compared with erythromycin against *C. pneumoniae* [16]. While the cost of azithromycin may exceed other macrolides, overall costs may be offset by decreased duration of therapy, lower preparation and administration costs, and reduced LOS [3,35].

Although the present study was designed to demonstrate equivalency rather than differences between ceftriaxone plus azithromycin and the comparator regimen, non-significant trends did emerge in terms of reduced duration of therapy and LOS that favoured ceftriaxone plus azithromycin. This was particularly evident for the 32% of patients from whom an atypical pathogen, or an atypical plus a typical pathogen, was isolated during the course of the study, with LOS being reduced by >3 days for patients treated with ceftriaxone plus azithromycin, compared with ceftriaxone plus clarithromycin/erythromycin. Furthermore, clinical success rates among patients with an atypical pathogen were greater in response to ceftriaxone plus azithromycin. Atypical pathogens such as *C. pneumoniae*, *M. pneumoniae* and *Legionella* spp. are implicated in up to 40% of CAP cases [5], further emphasising the need to provide adequate coverage during initial empirical therapy.

In conclusion, an intravenous-to-oral antimicrobial regimen of ceftriaxone plus azithro-

mycin appears to be at least as effective and well-tolerated as a standard regimen of ceftriaxone plus clarithromycin or erythromycin, and is a suitable treatment option for moderate-to-severely-ill patients hospitalised with CAP. Furthermore, ceftriaxone plus azithromycin may be a better treatment option in terms of reducing the duration of therapy and LOS, and may be associated with improved tolerance in patients switched to oral therapy. Further research is needed to confirm these findings.

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